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EXAMINER	
HILL, KEVIN KAI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,10-16,18,31,32,40,42,95,99 and 147-149* is/are pending in the application.

4a) Of the above claim(s) *3,5,10-16,18,32,40,42,95,99 and 147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,31,148 and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant has elected the invention of Group I, drawn to an immunomer compound comprising at least two oligonucleotides linked together, wherein Applicant has elected the oligonucleotide linkage species to be "iv", a sugar to a non-nucleotide linker and the "G" moiety species to be "2'-deoxy-7-deazaguanosine". However, upon further consideration, the Examiner has withdrawn the "G" species election requirement.

Election of Applicant's invention(s) was made without traverse.

Amendments

Applicant's response and amendments, filed September 4, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2, 4, 6-9, 17, 19-30, 33-39, 41, 43-94, 96-98 and 100-146, and withdrawn Claims 3, 5, 10-16, 18, 32, 40 and 42, 95, 99 and 147.

Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 31 and 148-149 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed parent provisional application 60/440,587 filed on January 16, 2003 under 35 U.S.C. 119(e) is acknowledged.

Accordingly, the effective priority date of the instant application is granted as January 16, 2003.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the September 4, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

1. **The prior rejection of Claims 1, 31 and 148 under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (2000; *of record in IDS) in view of Kandimalla et al (2001; *of record in IDS) and Liu et al (2001; *of record) **is withdrawn** in light of Applicant's argument that neither Yu et al, Kandimalla et al nor Liu et al teach the immunostimulatory

oligonucleotides to be linked at their 3' ends to a non-nucleotidic linker, as defined in the specification (pg 29, line 11-pg 31, line 14), which the Examiner finds persuasive. Yu and Kandimalla teach a "direct 3'-3' linkage (no linker involved)" for the purposes of the claimed invention (specification, pg 29, lines 14-16).

2. **The prior rejection of Claim 149 under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (Bioorg. & Med. Chem. 10:2585-2588, 2000; *of record in IDS) in view of Kandimalla et al (Bioorganic & Medicinal Chem. 9:807-813, 2001; *of record in IDS) and Liu et al (J. Mol. Biol. 308(3):465-475, 2001), as applied to Claims 1, 31 and 148 above, and in further view of Hutcherson et al (U.S. Patent 5,663,153) **is withdrawn** for reasons discussed above.

3. **Claims 1, 31 and 148 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (2000; *of record in IDS) in view of Kandimalla et al (2001; *of record in IDS) and Liu et al (2001; *of record) and Yu et al (N.A.R. 30(20):4460-4469, 2002; *of record in IDS).

This is a new rejection.

Determining the scope and contents of the prior art.

Yu et al teach an immunomer compound comprising at least two phosphorothioate (PS) oligonucleotides linked at their 3' ends, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprises an immunostimulatory C(ps)G dinucleotide motif, whereupon the PS-oligos that have their 3' ends blocked are very resistant to exonucleases and have higher immunostimulatory activity than non-linked oligos (pg 2587, Figures 2-3).

Yu et al do not teach the immunomer compound comprises a psC*psG dinucleotide motif illustrated in Figure 24 of the instant application. However, at the time of the invention, Kandimalla et al taught the synthesis of phosphorothioate CpG immunostimulatory oligonucleotides comprising a psC*psG dinucleotide motif, wherein the C* moiety represents a monocyclic or bicyclic cytosine analogue (pg 808, Figures 1 and 2) and the "G" moiety represents a guanosine or guanosine analogue, including 2' deoxyguanosine, 2'-deoxy-7-deazaguanosine, and other non-natural purine nucleosides (pg 809, Figure 3).

Neither Yu et al nor Kandimalla et al teach the cytosine is substituted for 2-oxo-7-deaza-8-methyl-purine (also known in the art as pyrrolocytosine). However, at the time of the invention, Liu et al taught the substitution of a cytosine for pyrrolocytosine in nucleic acid oligonucleotides.

Neither Yu et al nor Kandimalla et al teach the immunostimulatory oligonucleotides to be linked at their 3' ends to a non-nucleotidic linker, as defined in the specification (pg 29, line 11-pg 31, line 14). However, at the time of the invention, Yu et al taught the use of non-nucleotidic linkers that may be used in a 3'-3' configuration to link two oligonucleotides together (Figure 1).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in functional equivalents and analogues of nucleic acids and chemical synthesis of immunostimulatory oligonucleotides. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to substitute a first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a second bicyclic non-natural cytosine analogue having the structure shown in Figure 24 (Liu et al) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the prior art recognized that the P-base pyrrolocytosine (a.k.a. 2-oxo-7-deaza-8-methyl-purine) is a cytosine analogue. An artisan would be motivated to substitute a first bicyclic non-natural cytosine analogue as taught by Kandimalla et al with a second bicyclic non-natural cytosine analogue having the structure shown in Figure 24 because Liu et al teach that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it

ideal for probing protein-nucleic acid interactions (pg 466, col. 2, last ¶), i.e. the structure-immunostimulatory activity relationships of CpG oligos and the intracellular receptor/protein to which CpG oligos bind, triggering the immune cascade (Kandimalla), thereby providing the artisan a tool with which to study the not well-understood mechanism (Kandimalla) by which CpG oligonucleotide structures effect immunostimulatory activity.

It also would have been obvious to one of ordinary skill in the art to substitute the 3'-3' internucleoside linkage of Yu et al (2000) with a non-nucleotidic internucleoside linkage as taught by Yu et al (2002) with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute the 3'-3' internucleoside linkage of Yu et al (2000) with a non-nucleotidic internucleoside linkage because Yu et al (2002) taught the C3 linker achieves an improved immune response than an immunomer without a non-nucleotidic linker.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that Kandimalla does not provide the motivation to substitute cytosine with pyrrolo-dc. Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside (referred to as "the first bicyclic non-natural cytosine" by the Office Action) showed little or no immunostimulatory activity (see page 809, column 2, lines 22-24) (emphasis added). The Office Action fails to explain how one skilled in the art would be motivated, with a reasonable expectation of success, to make this "simple" substitution with a "second bicyclic non-natural cytosine" considering the first bicyclic non-natural cytosine was not

functional. At most, Kandimalla only adds an invitation "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it".

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner acknowledges the Kandimalla Declaration filed October 3, 2008 in which it is stated (¶5) that the phrase "showed little or no immunostimulatory activity" in reference to the P-base of Kandimalla (2001) meant that the modification was inactive. The motivation for an artisan to substitute the P-base of Kandimalla (2001) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 of the instant application is provided by Liu et al, who teach that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions (pg 466, col. 2, last ¶), i.e. the structure-immunostimulatory activity relationships of CpG oligos and the intracellular receptor/protein to which CpG oligos bind, triggering the immune cascade (Kandimalla), thereby providing the artisan a tool with which to study the not well-understood mechanism (Kandimalla) by which CpG oligonucleotide structures effect immunostimulatory activity.

Applicant argues that Liu is non-analogous art. The field of the present invention is oligonucleotide-based compounds that are immunostimulatory in mammalian systems. The intended use and/or purpose of Liu is to gain "an understanding of the nature of the melted bubble which moves with the RNA polymerase active site" during transcription elongation.

Applicant's argument(s) has been fully considered, but is not persuasive. "Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or application at issue] can provide a reason for combining the elements in the manner claimed. " *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). Thus a reference in a field different from that of applicant's endeavor may be reasonably pertinent if it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his or her invention as a whole. See MPEP §2141.01(a).

It is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741,82 USPQ2d 1385, 1396 (2007). See also Id. At 1742, 82 USPQ2d 1397 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

Liu et al is considered analogous art for teaching that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions.

Yu et al teach that their laboratory has been studying the impact of chemical modifications on the immunostimulatory activity of CpG oligos (pg 2585, col. 1). Similarly, Kandimalla et al teach that the mechanism of immunostimulation by CpG-oligonucleotides and the precise structural requirements and specific functional groups of cytosine and guanine necessary for recognition of and interaction with protein/receptor factors that are responsible for immune stimulation have not been elucidated (Abstract).

The problem in the field at the time of the invention comprises the elucidation of a structure/function relationship between a nucleic acid molecule and its protein receptor (Yu, Kandimalla). While Yu and Kandimalla teach assaying functional activity, neither teach measuring the ability of the oligonucleotides to bind to/interact with the protein receptor. Liu et al teach the artisan a means of assaying physical/structural properties [nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. The use of pyrrolocytosine (Liu) would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions [structural] in the presence **or absence** [emphasis added] of an immunostimulatory response [functional]. To put it another way, pyrrolocytosine (Liu) is recognized to be advantageous for detecting nucleic acid-protein physical interactions, regardless of the magnitude of the immunostimulatory response that may be undetectable or barely detectable.

With regard to substituting equivalents known in the prior art for the same purpose: Kandimalla et al taught the subustitution of a cytosine in a CpG motif for a P-base. Liu et al taught the substitution of a cytosine for the P-base, pyrrolocytosine. Thus, those of ordinary skill in the art recognized that cytosine may be substituted for pyrrolocytosine.

With regard to the selection of a known material [pyrrolocytosine (Liu)] based on its suitability for its intended use [detecting nucleic acid-protein interactions (Liu)] providing the artisan a tool with which to study the not well-understood mechanism (Yu, Kandimalla) by which CpG oligonucleotide structures effect immunostimulatory activity, the use of pyrrolocytosine would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions in the presence **or absence** [emphasis added] of an immunostimulatory response. To put it another way, pyrrolocytosine (Liu) is recognized to be advantageous for detecting nucleic acid-protein physical interactions, regardless of the magnitude of the immunostimulatory response that may be undetectable or barely detectable.

Applicant argues that Claim 18 recites a solution to the problem of providing new immunomer compounds comprising an immunostimulatory dinucleotide having the structure C*pG (wherein C*=R) while retaining (and modifying) immunostimulatory activity.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant is respectfully reminded that Claim 18 is presently withdrawn from examination, and thus will not be discussed further.

Applicant argues that there is no teaching or suggestion in Liu that pyrrolo-dc can be substituted in the CpG dinucleotide of a CpG-containing oligonucleotide while still maintaining the immunostimulatory properties of the oligonucleotide. Despite the fact that Liu is completely silent regarding immunostimulatory oligonucleotides, CpG motifs, or whether such a motif can be modified, particularly with pyrrolo-dc, and still retain its immunostimulatory activity, the Office Action states that one of skilled in the art would look to Liu in the context of CpG-containing oligonucleotides.

Applicant's argument(s) has been fully considered, but is not persuasive. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in

the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."). "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985)

In response to applicant's argument that there is no teaching or suggestion in Liu that pyrrolo-dc can be substituted in the CpG dinucleotide of a CpG-containing oligonucleotide while still maintaining the immunostimulatory properties of the oligonucleotide, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Yu et al teach that their laboratory has been studying the impact of chemical modifications on the immunostimulatory activity of CpG oligos (pg 2585, col. 1). Similarly, Kandimalla et al teach that the mechanism of immunostimulation by CpG-oligonucleotides and the precise structural requirements and specific functional groups of cytosine and guanine necessary for recognition of and interaction with protein/receptor factors that are responsible for immune stimulation have not been elucidated (Abstract). Kandimalla also teaches the substitution of a cytosine in a CpG motif for a P-base. Thus, at the time of the invention, the concept of a P-base substitution in a CpG motif was known.

The problem in the field at the time of the invention comprises the elucidation of a structure/function relationship between a nucleic acid molecule and its protein receptor (Yu, Kandimalla). Liu et al teach the artisan a means of assaying physical/structural properties [nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. The use of pyrrolocytosine (Liu) would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions [structural] in the presence **or absence** [emphasis added] of an immunostimulatory response [functional]. To put it another way, pyrrolocytosine (Liu) is

recognized to be advantageous for detecting nucleic acid-protein physical interactions, regardless of the magnitude of the immunostimulatory response that may be undetectable or barely detectable.

Applicant argues that one skilled in using oligonucleotides to induce an immune response in mammalian cells would not look to Liu's system for studying the melted bubble.

Applicant's argument(s) has been fully considered, but is not persuasive. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."). "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985)

The problem in the field at the time of the invention comprises the elucidation of a structure/function relationship between a nucleic acid molecule and its protein receptor (Yu, Kandimalla). Liu et al teach the artisan a means of assaying physical/structural properties [nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. The use of pyrrolocytosine (Liu) would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions [structural] in the presence **or absence** [emphasis added] of an immunostimulatory response [functional]. To put it another way, pyrrolocytosine (Liu) is recognized to be advantageous for detecting nucleic acid-protein physical interactions, regardless of the magnitude of the immunostimulatory response that may be undetectable or barely detectable.

Applicant argues that Kandimalla demonstrated that a first bicyclic non-natural cytosine substitution for C of the CpG was inactive (i.e., that the oligonucleotide of Kandimalla did not functionally interact with the protein receptor). Therefore, one skilled in the art would not be motivated to look to Liu's method, with a reasonable expectation of success, to use a second bicyclic non-natural cytosine to bind the TLR-9 receptor and be useful.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner acknowledges the Kandimalla Declaration filed October 3, 2008 in which it is stated (¶5) that the phrase "showed little or no immunostimulatory activity" in reference to the P-base of Kandimalla (2001) meant that the modification was inactive. The Kandimalla Declaration does NOT state that the P-base containing oligonucleotide failed to **physically** [emphasis added] interact with the protein receptor, only that the oligonucleotide showed little or no immunostimulatory activity. However, the motivation for an artisan to substitute the P-base of Kandimalla (2001) with a bicyclic non-natural cytosine analogue having the structure shown in Figure 24 of the instant application is provided by Liu et al, who teach that pyrrolocytosine is advantageous because it is intrinsically highly fluorescent, with excitation and emission maxima far from those of DNA and protein, making it ideal for probing protein-nucleic acid interactions (pg 466, col. 2, last ¶), i.e. the structure-immunostimulatory activity relationships of CpG oligos and the intracellular receptor/protein to which CpG oligos bind, triggering the immune cascade (Kandimalla), thereby providing the artisan a tool with which to study the not well-understood mechanism (Kandimalla) by which CpG oligonucleotide structures effect immunostimulatory activity.

The problem in the field at the time of the invention comprises the elucidation of a structure/function relationship between a nucleic acid molecule and its protein receptor (Yu, Kandimalla). Liu et al teach the artisan a means of assaying physical/structural properties [nucleic acid-protein interactions] which complements the functional assays taught by Yu et al and Kandimalla et al. The use of pyrrolocytosine (Liu) would have logically commended itself to an inventor's attention because it advantageously provides a means of detecting nucleic acid-protein interactions [structural] in the presence **or absence** [emphasis added] of an immunostimulatory response [functional]. To put it another way, pyrrolocytosine (Liu) is recognized to be advantageous for detecting nucleic acid-protein physical interactions, regardless

of the magnitude of the immunostimulatory response that may be undetectable or barely detectable.

4. **Claim 149 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Yu et al (2000; *of record in IDS) in view of Kandimalla et al (2001; *of record in IDS), Liu et al (2001; *of record) and Yu et al (N.A.R. 30(20):4460-4469, 2002; *of record in IDS), as applied to Claims 1, 31 and 148 above, and in further view of Hutcherson et al (U.S. Patent 5,663,153; *of record).

This is a new rejection.

Neither Yu et al (2000), Kandimalla et al, Liu et al nor Yu et al (2002) teach an immunomer compound consisting essentially of phosphorothioate internucleoside linkages. However, at the time of the invention, Hutcherson et al disclose immunostimulatory oligonucleotides consisting essentially of phosphorothioate internucleoside linkages.

It would have been obvious to modify the immunostimulatory oligonucleotides comprising phosphorothioate internucleoside linkages of Yu et al in view of Kandimalla et al and Liu et al to consist essentially of phosphorothioate internucleoside linkages as taught by Hutcherson et al with a reasonable expectation of success because Hutcherson et al successfully demonstrated that oligonucleotides consisting essentially of phosphorothioate internucleoside linkages possess immunostimulatory activity.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Double Patenting

5. **Claim 1 stands provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 1 of copending Application No. 10/361,111 (U.S. 2004/0156825).

Note: A Notice of Allowance of Claim 1 of 10/361,111 was mailed December 21, 2007.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is modified, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside. Thus, although the subject matter is recited using different terms, the composition(s) of the instant claim(s) is reasonably embraces and anticipates the composition(s) recited in the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

6. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 18 of copending Application No. 10/865,245.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

The claims are drawn to an immunostimulatory oligonucleotide compound comprising a "CpG" motif, wherein the "C" moiety is a non-natural pyrimidine and the "G" moiety is a natural or non-natural pyrimidine nucleoside, wherein the immunostimulatory oligonucleotides may be joined by 3' to 3' linkages. Thus, instantly claimed immunomer composition(s) are reasonably embraced by immunostimulatory oligonucleotide(s) of the copending application. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

7. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 11-13 and 16 of copending Application No. 11/153,054.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Because the claims of copending Application No. 11/153,054 recite generically "CpG, C*pG, C*pG* and CpG*", the Examiner has looked to the specification for definitions of the "C" and "G" moieties so as to better understand the invention. The specification discloses that C* is… 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine, and that G* is… 2'-deoxy-7-deazaguanosine (pg 1, [0010]), wherein the non-nucleotidic linker may be a 3'-3' linkage (pg 3, [0032]). Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

8. **Claims 1 and 31 stand provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1 and 4 of copending Application No. 11/174,002 (U.S. 2006/0211641).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a natural or non-natural purine nucleoside.

Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Response to Arguments

Applicant argues that Applicants will consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications 10/361,111, 10/865,245, 11/153,054 and 11/174,002.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant has not filed a Terminal Disclaimer or taken any other action deemed necessary in the later filed, copending applications as it pertains to the instant application. The provisional nonstatutory

obviousness-type double patenting rejections will be maintained until all claims have been deemed otherwise in condition for allowance or allowable.

Conclusion

9. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Krieg et al (U.S. 2004/0053880 A1) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with a P-base [0094].

Fearon et al (U.S. Patent 7,255,868) disclosed immunostimulatory nucleic acids comprising CpG motifs, wherein the cytosine may be substituted with an isostructural bicyclic analog (col. 30, line 45-col. 31, line 40).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633